

Transcranial Magnetic Stimulation: Decomposing the Processes Underlying Action Preparation

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Abstract

Preparing actions requires the operation of several cognitive control processes that influence the state of the motor system to ensure that the appropriate behavior is ultimately selected and executed. For example, some form of competition resolution ensures that the right action is chosen among alternatives, often in the presence of conflict; at the same time, impulse control ought to be deployed to prevent premature responses. Here we review how state-changes in the human motor system during action preparation can be studied through motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation over the contralateral primary motor cortex (M1). We discuss how the physiological fingerprints afforded by MEPs have helped to decompose some of the dynamic and effector-specific influences on the motor system during action preparation. We focus on competition resolution, conflict and impulse control, as well as on the influence of higher cognitive decision-related variables. The selected examples demonstrate the usefulness of MEPs as physiological readouts for decomposing the influence of distinct, but often overlapping, control processes on the human motor system during action preparation.

Keywords

action selection, action preparation, decision making, motor inhibition, motor excitability, movement, motor cortex, premotor cortex

Introduction

Many of our daily behaviors require navigating through continuous sets of action choices (Cisek 2007), such as taking a cup of coffee from a table, preparing to serve during tennis, or avoiding a fast approaching car. In all these situations, we face the problem of having to prepare an appropriate response from several alternatives. However, the seemingly fluid and effortless manner with which we pick up a cup of coffee contrasts with the complexity of the underlying neural operations even in this simple action. Grasping a cup is influenced, for example, by the relative position of the two hands with respect to the object, the shape of the cup and the orientation of its handle, contextual rules (“Is there another object in front of the cup?”, “Is this my cup?”), and previous experience (“Have I picked up this cup before?”, “Is it likely to be hot?”).

In this article, we review and discuss the usefulness of transcranial magnetic stimulation (TMS) to identify different cognitive control processes that jointly contribute to action preparation. In the following, we will use the term *action preparation* as shorthand to describe processes that occur prior to the actual execution of actions. However, we point out that action preparation is not a

unitary process but instead is composed of several cognitive control mechanisms that are colloquially summarized as “preparation” or “planning” (Wong and others 2014). One challenge in humans is thus to isolate and characterize the relative contributions that different computations have on the state of the motor system during action preparation (Fig. 1).

One fruitful approach to address this challenge with TMS is through quantification of motor-evoked potentials (MEPs), which can be elicited in contralateral hand muscles when applying TMS over primary motor cortex (M1; Box 1). MEPs can provide a temporally precise and muscle-specific readout of state-changes in the motor system before, during, and after motor behavior. While

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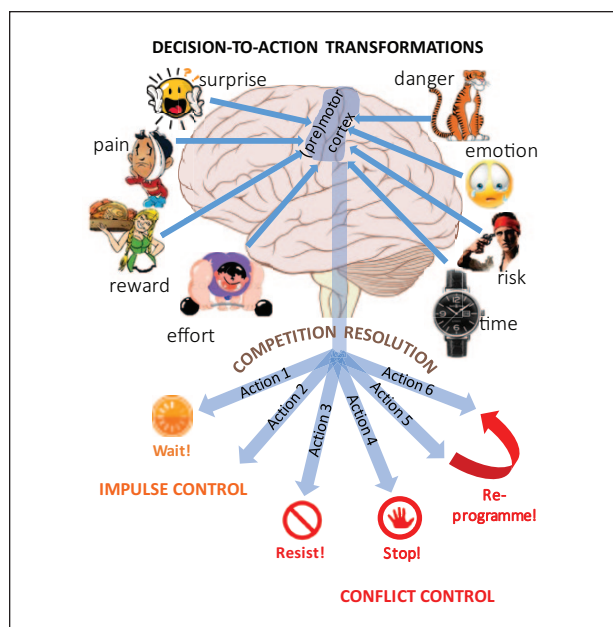


Figure 1. Decision to action mapping. Dynamic changes in our environment and our movement intentions require constant revision of the best course of action. This revision is influenced by any process that in a given context provides meaningful information in favor of one action over another, and thus helps specify which opportunities for action should be realized. The challenge then is to select between different opportunities for action, and to prepare one action over its alternatives. This latter challenge is thought to engage several cognitive control processes that ultimately integrate to select an action. At any point in time, several variables may provide information for which action to select. This information, however, can be conflicting, or require rapid revision of ongoing estimates about the best course of action. As a consequence, there is a constant “tug-of-war” between competing action representations, which is fueled by evidence from various sources and brain regions that seek to ensure the correct action is selected, at the right time. This illustrates a key challenge for studies seeking to assess how actions are prepared—the simultaneous occurrence of distinct processes that exert overlapping influences over action representations in the motor system.

we note that the precise mechanisms underlying MEPs remain subject of investigation (Bestmann and Krakauer 2015; Di Lazzaro and Rothwell 2014), for the remainder of this article we assume that MEPs quantify and track state-changes in the human motor system, and provide an assay of action representations at the level of (pre)motor cortex. Moreover, we use action representation here as shorthand for the neural elements controlling one action over another, at least at the level of changes we can assess with TMS. We will not, however, assume that this readout indicates any causal relationship between the state-changes that it reflects and concomitant behavior (cf. Bestmann and Krakauer 2015).

Box 1. Transcranial Magnetic Stimulation (TMS).

Transcranial magnetic stimulation allows for noninvasive stimulation of cortical tissue through the intact scalp of a participant. The technique induces a short-lived ($\sim 200 \mu\text{s}$) electrical current of up to 5 kA in a stimulation coil placed over the scalp of the participant, which in turn will generate a perpendicular magnetic field (i.e., directed to the cortex) proportional to the intensity and duration of this current. This magnetic field penetrates the scalp and underlying tissue without restriction, and in turn will induce a current in cortex which is perpendicular to the induced magnetic field (i.e., parallel to the stimulation coil). This cortical current is proportional to the strength and rate of change of the induced magnetic field. But critically, the cortical current is several orders of magnitude weaker than the current in the stimulation coil, though it is of sufficient strength to activate the axons of neurons in the cortex and underlying subcortical white matter underneath the stimulation coil.

When applied over primary motor cortex (M1), TMS can elicit descending volleys in corticospinal projections, which in turn can activate the spinal motoneurons that innervate peripheral muscles contralateral to the stimulation site (see Fig. 2). The cortical representations of the intrinsic hand muscles have the lowest threshold for stimulation. The evoked muscle response, the so-called motor-evoked potential (MEP), can easily be recorded using surface electromyography (EMG), lending it nicely to investigation of simple manual movements and dexterous control. However, TMS predominantly activates fast-conducting crossed corticospinal fibers, and thus MEPs only reflect a part of descending projections that contribute to the control of movement (cf. Bestmann and Krakauer 2015; Di Lazzaro and Rothwell 2014; Di Lazzaro and Ziemann 2013, for reviews).

Moreover, a single TMS pulse can excite myriads of cortical fibers that in turn project onto corticospinal neurons. These projections can originate in M1 intracortical circuits, or they may come from other areas such as premotor, somatosensory or parietal regions through transcortical circuits possibly involving also prefrontal areas (Bestmann and Krakauer 2015). In addition, because the corticospinal cells synapse onto motoneurons in the spinal cord before reaching their targeted muscle, the MEPs will also reflect the excitability of the spinal circuitry. Hence, the bipolar MEP measured with surface electromyography from peripheral muscles is in essence a low-pass filtered signal resulting from a complex series of waves that descend through the corticospinal tract (so-called D- and I-waves; Di Lazzaro and Rothwell 2014) and then is passed onto spinal motoneurons. Each of these waves is potentially influenced by different circuits and inputs.

Relevant to the current issue is that these inputs provide routes through which different processes and computations can exert their influence on the motor system. Because a single TMS pulse is short ($\sim 250 \mu\text{s}$), the temporal precision with which TMS can probe these influences is excellent. How different processes might influence the motor system at the time of stimulation can thus be reflected in amplitude changes of MEPs, and/or their variability (Klein-Flügge and

others 2013). Transcortical projections might play a crucial role in the context-dependent state-changes commonly observed in MEPs during action preparation.

One additional advantage of TMS is that one can employ protocols that allow for probing the state of several of the outlined circuits directly and selectively. For example, conditioning-test, or so-called paired-pulse protocols (Kujirai and others 1993) apply a low-intensity sub-threshold conditioning TMS pulse, and measure its impact on the MEP response evoked by a subsequent supra-threshold test pulse generated in the same coil. The two TMS pulses are applied over M1 not only at specific intensities but also at specific times. For example, conditioning pulses applied between 2 and 5 ms or between 50 and 200 ms before the test pulse are thought to probe GABAergic intracortical inhibitory circuits, thus providing an assay to link inhibitory neurotransmission with motor behavior.

This is of relevance as different assays of inhibitory and excitatory circuits undergo distinct changes during different tasks and contexts. For example, so-called short intracortical inhibition (SICI), which is thought to tap into GABA_A receptor driven neurotransmission (Di Lazzaro and Rothwell 2014) is reduced for prepared actions (Duque and Ivry 2009; Sinclair and Hammond 2008, 2009). Similarly, long ICI (LICI; Opie and others 2014; Sinclair and Hammond 2008) is thought to probe GABA_B receptor driven neurotransmission (Di Lazzaro and Rothwell 2014), and has been associated with other aspects of action preparation. More recently, Hamada and others (2014) have reported an elegant series of experiments in which they reversed the direction of current flow induced by TMS to probe distinct interneuron circuits (Di Lazzaro and Ziemann 2013). This was combined with paired associative stimulation, another form of paired-pulse stimulation, to demonstrate that these separate M1 intracortical circuits respond to different forms of motor learning. We point out that changes in inhibition and excitation as cellular phenomena are inferred from the expression of an electrophysiological phenomenon (i.e., a change in MEP amplitude under a specific TMS protocol). The mapping between the cellular process and the physiological read-out, however, is incompletely understood and by no means transparent.

In conclusion, different TMS protocols provide for a rich arsenal of ways to selectively probe circuits that may be involved in action preparation, and perhaps even more specifically, to study the influence exerted by specific cognitive control processes on the human motor system.

Cognitive Processes for the Control of Action Preparation

Successful preparation requires several cognitive control mechanisms (Rushworth and others 2009) that together enable us to select, specify and execute actions in a dynamic manner (Cisek 2012). Traditionally, perception, cognition and action have been conceptualized as distinct and serial processes, whereby the analysis of sensory information and decision making is completed

before actions are prepared and executed. However, our brain does not adhere to this clear-cut separation (Cisek 2012; Selen and others 2012; Thura and Cisek 2014). Instead, the influence of different processes is thought to occur in a continuous, parallel fashion, whereby several regions influence a continuous tug-of-war between different action representations in the motor cortex, to determine the action associated with the most relevant and valuable outcome. These processes are likely to change their allegiance with a specific action from one moment to another if contextual changes demand so. Consequently, one may expect that action representations are continuously shaped by the outcome of this dynamic competition, and that MEPs elicited with TMS over M1 may thus provide suitable readouts of the dynamic changes occurring during action preparation (Bestmann and Krakauer 2015). Because in many situations several control processes are likely to exert their influence on the motor system at the same time (Fig. 1), sometimes in antagonistic fashion, it remains a challenge to divorce their influences on the motor system.

Here, we focus on a set of processes that have frequently been investigated using TMS, including *competition resolution*, which resolves which action to choose among possible alternatives; *impulse control*, which prevents actions from being unleashed prematurely; and some form of inhibition that deals with *conflict* arising from irrelevant information, or from unexpected changes in our environment that require rapid adaptation of prepared actions.

Competition resolution is the process through which we resolve which action to choose in a goal-directed and context-dependent way, through gradual elimination of response alternatives. We furthermore are often faced with the requirement to withhold or postpone an action, an ability which relies on impulse control preventing movements from being prematurely released. In other situations sensory information can interfere with this process and trigger alternative behaviors. The suppression of these conflicting actions is thought to rely on inhibitory control processes that prevent us from behaving in an “automatic,” stimulus-driven manner. Moreover, in a dynamic environment, sensory information can suddenly change and require us to terminate the currently prepared movement, while specifying another action mandated by the newly available information. In some cases, environmental changes may even require us to abandon, or stop, the action altogether. Stopping is thought to rely on dedicated circuits in the brain (Aron 2011) and poses specific requirements to the motor system, which are thought to be distinct from other cognitive processes concerned with conflict resolution.

We argue that different cognitive systems often deploy their influence simultaneously, yet often with different functional purposes. This raises the question of how one might disentangle the relative influence that these systems exert on action representations in the human brain?

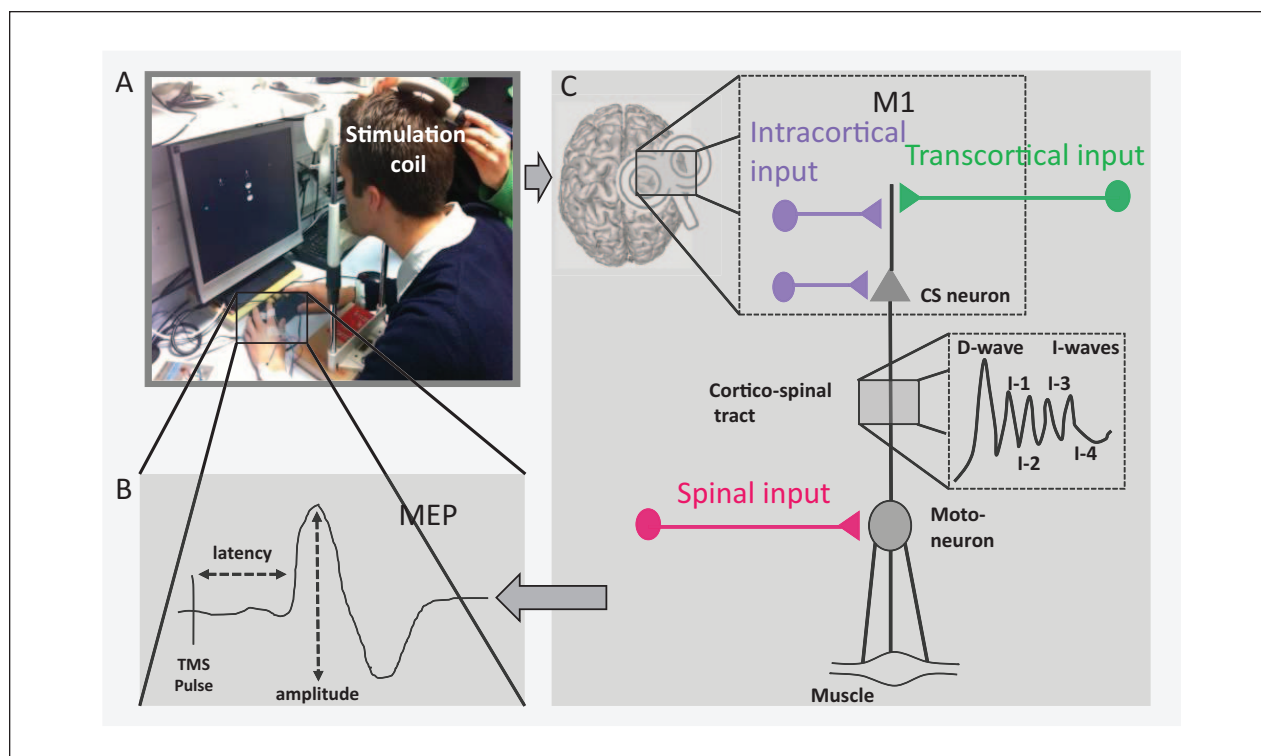


Figure 2. Assessing the state of human action representations with transcranial magnetic stimulation (TMS) over primary motor cortex (M1). (A) Example of a TMS coil placed over the right M1 in a participant performing a task. Motor-evoked potentials (MEPs) are recorded via surface electrodes. (B) The MEP is a biphasic component, whose peak-to-peak amplitude reflects corticospinal (CS) excitability at the time of stimulation. (C) A single TMS pulse over M1 can activate CS neurons directly or indirectly, via the activation of intracortical circuits projecting in turn onto CS neurons. Besides, transcortical inputs from premotor, prefrontal and parietal cortices can also be activated by TMS over M1. Hence, depending on the intensity of stimulation and the specific structures activated by TMS, a series of descending volleys occurs along the CS neurons, that are due to the direct (D) or indirect (I) activation of CS neurons. Importantly, these D- and I-“waves”, together with additional spinal contributions, have distinct generators that jointly give rise to the MEP recorded from muscles contralateral to the stimulation.

They often overlap in time, yet ultimately influence action representations at some point during preparation. Preparation can thus likely be decomposed into several subprocesses, which jointly contribute to the signatures of preparation often observed.

In the following, we show that TMS in humans provides a way to identify some of the contributions different brain regions and processes exert during preparation. TMS provides dissociable physiological fingerprints of the psychological processes at play in the motor system during action preparation, and MEPs offer a unique opportunity to quantify state-changes there in a dynamic and effector-specific way (Fig. 2; Box 1).

Using MEPs to Quantify State-Changes in the Human Motor System during Action Choices

Many situations in daily life require choosing between competing actions (Duque and others 2014). Mechanistically,

competition resolution is thought to arise in a winner-takes-all fashion, where the action that “wins” a competitive process among alternatives is finally executed. Indeed, neural recordings from dorsal premotor cortex in nonhuman primates provide support for this idea (Cisek and Kalaska 2005; Cisek and Pastor-Bernier 2014). When evidence is gathered that favors one action over another, the firing rates of dorsal premotor (PMd) neurons coding for that action steeply increase, whereas firing rates of neurons responding preferentially for the alternative action are suppressed. This antagonistic development in firing rates is thought to be controlled by some form of mutual inhibition between different action representations. If MEPs reveal something about competition resolution, one might expect them to undergo qualitatively similar changes to those observed in animal recordings, when comparing selected and nonselected action representations.

Transcranial magnetic stimulation studies in humans have shown such antagonistic MEP amplitude changes during action preparation, which are qualitatively consistent

with neural recordings in nonhuman primates. During reaction time (RT) tasks, for example, a motor response is generated as fast as possible following an imperative signal; here, TMS is usually applied at several time points between the signal and the movement onset, and changes in MEP amplitudes indeed track the unfolding of the preparation process (Chen and Hallett 1999; Davey and others 1998; Leocani and others 2000). In the simplest version of these RT tasks, the imperative (“Go”) signal always specifies the same movement. Preceding such movements, there is a gradual increase in the amplitude of MEPs recorded in the agonist muscle, starting approximately 100 ms prior to the onset of the volitional EMG (Chen and Hallett 1999; Chen and others 1998; Leocani and others 2000; Starr and others 1988), and possibly arising from a release of intracortical inhibition (Reynolds and Ashby 1999).

In more complex versions of the RT task, the imperative signal requires choosing between a set of predefined options (e.g., a left- or right-hand finger response), hence allowing for the investigation of the correlates of competition resolution on motor preparatory changes for agonist muscles in both the selected and nonselected hands (Fig. 3). Interestingly, MEPs are often suppressed in the nonselected hand (Burle and others 2004; Duque and others 2005; Leocani and others 2000; Tandonnet and others 2011) and this suppression likely arises at the cortical level. Such a suppression is often either not seen, or is much less pronounced, when the resting hand is not part of the initial response set (Leocani and others 2000), suggesting the operation of a process through which the competition between selected and nonselected action representations is resolved, by antagonistically controlling their preparatory state.

We note that, although competition resolution often occurs in the context of specific postural requirements, the relationship between these two coexisting processes has not been investigated so far. In addition, it remains currently unresolved how state-changes during preparation relate to those during the execution of an action (see Box 2). In other words, to date, the use of average MEP changes alone has not allowed to capture a straightforward relationship between these two phases.

Using MEPs to Quantify State-Changes in the Human Motor System during Impulse Control

Many situations require the suppression of selected responses for a certain period of time in order to prevent their premature initiation. Such impulse control is distinct from competition resolution which rather involves the suppression of nonselected responses (Fig. 4). So-called instructed-delay tasks, in which an informative cue is followed by some delay period and a subsequent imperative

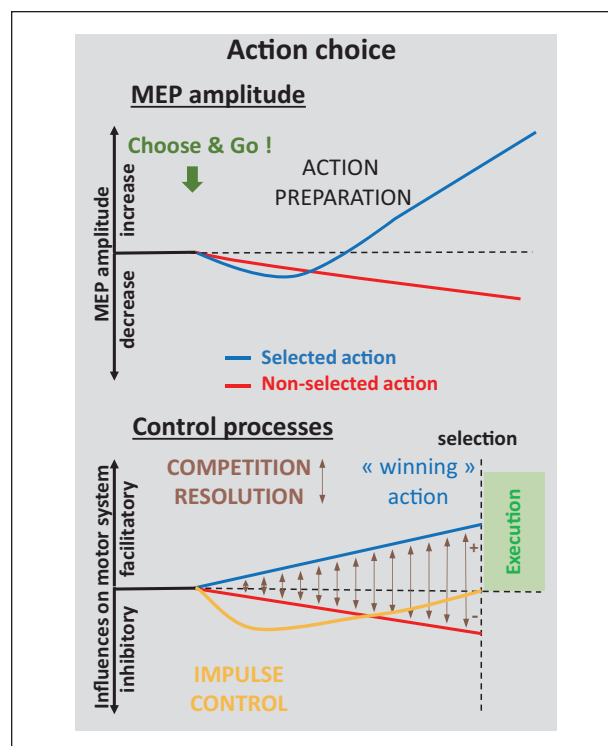


Figure 3. Hypothetical motor-evoked potential (MEP) changes and some of the relevant control processes during action choices. During action choices, MEPs elicited at the beginning of a trial are often suppressed relative to baseline. This suppression is commonly observed for both the selected and nonselected actions; it is in fact sometimes even larger for the selected response, relative to the nonselected one. This possibly reflects the faster deployment of the impulse control inhibition (predominantly directed at selected actions) compared with the inhibition for competition resolution (predominantly directed at nonselected actions), which becomes stronger as the competitive process develops. Closer to the actual response there is a gradual increase in the amplitude of selected MEPs, while the nonselected MEPs become progressively more suppressed, thus amplifying the difference between the two competing action representations. Competition resolution as illustrated here is thought to arise from the antagonistic regulation of competing action representations, which facilitates activation of the action that should be selected and inhibits the alternative. Concurrent to this process, impulse control is thought to employ an inhibitory influence, possibly to minimize the risk of a premature release of the currently “winning” action while the competition runs its course. The timeline is for illustration purposes only and does not reflect the true time course of process deployment.

(“go”) stimulus, allow for assessing how impulse control shapes motor activity. Studies in nonhuman primates have shown that neurons in (pre)motor cortex representing the selected action increase their firing rates during such delay periods (Cisek and Kalaska 2005), whereas

Box 2. Methodological Considerations and Outstanding Questions.

One limitation of TMS MEP studies is that the MEP is a pointwise readout of state-changes, but this readout can, in principle, be influenced by multiple co-occurring or temporally overlapping processes (Duque and others 2010). Relating changes in MEP amplitude to a specific phenomena or computation can thus be fraught with complication. With relevant to the examples discussed here we point out that currently the full time courses of MEP changes as indicated in Figures 3 to 7 have not been explored in combination and with careful isolation of the different processes that may co-occur throughout. The time courses of MEP changes shown in this article thus remain, at least to some extent, speculative, but nevertheless serve to highlight how the dynamic changes of action representations depend on various processes at play.

The examples provided do, however, illustrate how complex machinery behind action preparation can be decomposed. Key to this is the use of careful experimental designs that in principle allow for independently manipulating different cognitive processes likely to be involved in a given task. Whether an observed MEP change is specific to competition resolution or impulse control, for example, may require the measurement of the nonselected muscles as well as the comparisons with contexts in which impulse control, or competition resolution, is less (or more) required.

Motor-evoked potential measures acquired only at a single time point and for a single muscle are thus unlikely to divorce influences from different processes. Because the temporal profile of such influences and thus their impact on MEPs is distinct, a more fine-grained sampling of MEP changes over time can start to isolate the relative contribution of different cognitive systems. For example, global stopping influences both selected and nonselected action representations, whereas competition resolution is thought to act antagonistically on selected and nonselected action representations. Thus, comparison of both agonistic and antagonistic muscle representations, ideally at different points throughout a trial, can help distinguish between both facilitatory and inhibitory cognitive processes acting at the same time.

This also means that increases in MEPs could arise from an increase in excitability, or through a more specific release from inhibition, occurring in the intracortical and transcortical circuitry. While the resultant MEP could look identical, the underlying cause would be distinct physiological and cognitive mechanisms. Paired-pulse procedures can selectively probe specific intracortical and transcortical circuits, and thus distinguish between these alternative explanations.

We also note that processes such as attention, vigilance, or arousal are required in many tasks, and for this reason, comparisons with resting baseline periods can be troublesome. Comparison of MEP changes throughout a trial may provide a better control for these processes (Bestmann and Krakauer 2015).

Double-coil protocols provide an additional way to decompose processes that influence the motor system during preparation (Hasan and others 2013). These studies apply a conditioning pulse over one cortical region, and measure its impact on TMS pulses applied over M1. Provided prior knowledge exists about the specific functional role of a cortical region, this approach offers to isolate the specific influence of transcortical projections on action representations in (pre)motor cortex. Moreover, identifying the specific timing at which this influence occurs can provide a further means for isolating specific component processes influence preparation.

Notably, most action choices occur in parallel with postural control. Yet, how competition resolution interacts with postural control has not been investigated so far and deserves some future attention. For example, it is unclear how MEP suppression in a nonselected hand is influenced by postural constraints the task may impose on that hand. In particular, one may expect MEP suppression to be attenuated when a nonselected muscle has to become/remain active to play a supporting role.

Finally, it is currently unclear how MEP changes observed prior to movement relate to the changes occurring during the execution of a prepared action. In other words, if the specific patterns of MEP changes observed during preparation indeed provide readouts of successful response preparation and selection, then one may expect these to relate closely to the changes occurring during the execution of that response. For example, if MEP changes observed in selected and nonselected muscles are taken as indication for competition resolution, does this allow prediction of the pattern of changes occurring following movement initiation and how the movement is executed? Currently, these questions remain unresolved, but a possible independence of MEP changes prior to and during movement would suggest that MEPs are useful assays for identifying the contribution of different processes onto the motor system, but do not disclose how these processes contribute to the actual execution of an action.

neurons corresponding to nonselected actions often decrease during the delay. This observation has been interpreted as a physiological correlate of advanced action preparation, and one might expect these changes in firing rates to be mirrored by corresponding changes in MEP amplitude for selected and nonselected actions during delay periods.

Interestingly, MEPs are often suppressed, relative to some baseline, when preparing a movement in anticipation of an imperative signal (Duque and Ivry 2009; Greenhouse and others 2015; Hasbroucq and others 1997; Lebon and others 2015; Touge and others 1998). This decrease is generally strongest just before the expected time of the imperative signal, particularly when its onset and identity can be accurately predicted (Davranche and others 2007; Hasbroucq and others

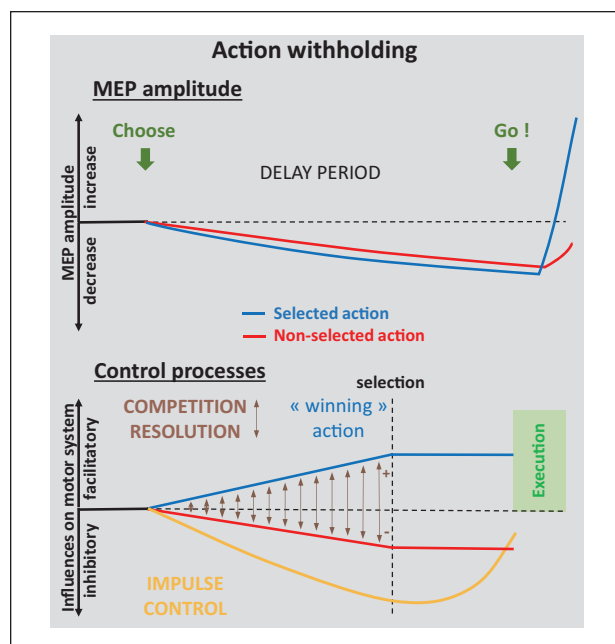


Figure 4. Hypothetical motor-evoked potential (MEP) changes and control processes during action withholding. Impulse control is commonly studied in tasks that explicitly require subjects to withhold a planned action. During the delay period in these tasks, the selected effector needs to remain silent although its cortical representation becomes facilitated by the competition resolution process, in anticipation of the imperative signal. The ability to withhold a response in this context is thought to rely on an inhibitory process that allows the facilitatory control of the “winning” action while preventing the engagement of the peripheral motor system. MEPs from the selected hand are often suppressed during delay periods and this effect is most pronounced immediately before the expected time of the go signal. Interestingly, this MEP suppression (putatively reflecting impulse control) is often more pronounced than that observed in association with a nonselected action (putatively reflecting competition resolution). Note that this effect can also be observed during competition resolution when there is no need to postpone response initiation (as illustrated in Fig. 3). This suggests that impulse control is deployed as soon as motor representations become activated, providing a safeguard against premature responses. The timeline is for illustration purposes only and does not reflect the true time course of process deployment.

1999), but less so for prolonged delay periods or unpredictable imperative stimuli (Mars and others 2007; van den Hurk and others 2007). Moreover, MEP suppression is often observed for both selected and nonselected responses. This may result from the operation of an inhibitory process that more broadly and nonspecifically exerts its influence during delay periods.

Alternatively, two distinct inhibitory mechanisms may coexist that both suppress MEPs, one acting on selected and another one acting on nonselected action representations, with different functional purposes (Fig. 4) (Duque and others 2010; Duque and others 2012; Lebon and others 2015). The inhibitory effect observed for nonselected actions may relate to competition resolution (Bestmann and others 2008) and reflects the suppression of alternative but unwanted action representations, similar to the effect observed after imperative signals in choice RT tasks (Burle and others 2004; Duque and others 2005; Greenhouse and others 2015). That is, because the precue indicates the required response, participants can inhibit the nonselected responses in advance of the imperative signal. Consistent with this view, it was recently shown that the amount of MEP suppression in nonselected muscles during delay periods depends on the anatomical and/or functional relationship between the competing effectors (Labruna and others 2014). Such a competition-dependent effect was not observed for the selected MEPs, suggesting a separate origin for the MEP suppression observed in that condition.

The suppression of the selected response representation seems to be directly related to impulse control. Speculatively, this inhibitory process may allow activity to be tuned by central planning processes in order to prepare the system for the required forthcoming action, whilst preventing the engagement of the peripheral motor system during a delay period. Consistent with this idea, the amplitude of MEPs in selected muscles during the delay period reflects contributions from cortical excitatory (dis-inhibitory), and spinal inhibitory influences acting simultaneously on the motor output system (Davranche and others 2007; Duclos and others 2008; Duque and Ivry 2009; Duque and others 2010; Duque and others 2012; Hasbroucq and others 1999; Sinclair and Hammond 2008; Touge and others 1998). The primate literature has also reported inhibitory influences acting at the spinal level during delay periods (Prut and Fetz 1999). Such distinct contributions to MEP changes in humans have been identified by using additional neurophysiological approaches, including Hoffman reflexes, which provide a measure of spinal excitability, and paired-pulse TMS protocols that allow for the specific investigation of the M1 neural circuitry (see Box 1 and Fig. 2).

Notably, when there is no informative cue to announce the time and the requirements of the imperative signal, a brief initial inhibition of the selected action representation can be observed just after the imperative signal occurs, even if there is no need to delay response initiation at this time (Duque and others 2014). Hence, the inhibition of selected representations does not seem to be solely related to the goal to postpone a response until the

end of a delay period, but may reflect the operation of an impulse control mechanism that is automatically engaged during action selection. This may provide a safeguard against premature execution of the required movement until enough information has been gathered to commit to an action. Further studies are required to understand the neural routes involved in the inhibition of selected responses. Potential candidates are the dorsal premotor cortex and the indirect basal ganglia pathway (Aron 2011; Duque and others 2012).

Using MEPs to Quantify State-Changes in the Human Motor System in the Presence of Conflict

In many situations, the dynamic changes in our environment can create conflicts with currently planned actions. We briefly review key results on MEP changes during three types of conflict: conflict arising from (1) goal-irrelevant sensory information, and conflict due to changes in the environment requiring either (2) reprogramming or (3) stopping a prepared action that the studies reviewed here will serve as selected examples about the influence that these processes exert on MEPs.

Conflict Arising from Goal-Irrelevant Sensory Information

A frequent source of conflict during action preparation arises from goal-irrelevant information (Cohen and others 1990). The degree to which such information delays response times provides a sensitive quantitative measure of an individual's ability to engage suppression of inappropriate responses (Verleger and others 2009). This raises the question as to how goal-irrelevant information, and the suppression thereof, may influence action representations. One way to test this is by manipulating the proportion of trials in which so-called visual distractor stimuli either indicate the same response as the imperative visual stimulus (congruent trial), or the opposite response (incongruent trial). When the majority of trials are incongruent ("Mostly incongruent" MI context), subjects likely anticipate the occurrence of conflicting information in most trials; by contrast, when the majority of trials is congruent ("Mostly congruent" MC context), the expectation of conflict ought to be low.

Recent work (Klein and others 2014) shows that in these situations, MEPs elicited from inappropriate response representations are larger in incongruent compared to congruent trials, consistent with a larger conflict level in the former type of trials (Michelet and others 2010; van Campen and others 2014; Verleger and others 2009). Interestingly, this effect is only present in an MC context, a condition in which the requirement for conflict

regulation is presumably marginal because subjects have the overall expectation that conflict trials are rare (Botvinick and others 1999; Ridderinkhof 2002). By contrast, when conflict is strongly expected (MI context), inappropriate response representations during incongruent trials are relatively suppressed. This might provide indication that inhibitory control is deployed mainly when conflict is expected, to reduce the inappropriate activation of unwanted motor representations.

It is worth mentioning that the occurrence of irrelevant motor activations in the presence of conflict is at odds with the observation that relevant representations are actually suppressed during the early stage of movement preparation. As explained in the previous section, the latter suppression has been related to the recruitment of impulse control influences to provide a safeguard against premature movements until enough information is gathered to commit to an action. But then the question arises as to why irrelevant representations are not (or less) subject to such influences, an issue for future investigations. Importantly, studies that have quantified MEPs changes during conflict resolution have commonly not reported the (impulse control) inhibition of the selected action that is often observed in no-conflict trials (Michelet and others 2010).

Conflicting sensory information thus directly affects the representation of actions involved in the task (Fig. 5). In the example given here, pre-supplementary motor area (Duque and others 2013; Taylor and others 2007) or lateral prefrontal cortex (Duque and others 2012) have been identified as key regions to help resolve this decision, possibly by exerting additional inhibitory influences over unwanted motor representations in M1, a process that needs to be confirmed in further experiments.

Conflict Arising from New Sensory Information that Requires Action Reprogramming

Another form of conflict arises when changes in our environment demand rapid adjustment of our planned actions. A tennis player anticipating a ball, for example, will have to rapidly adjust his planned movement when the ball unexpectedly grazes the net and thus changes its trajectory. The *reprogramming of actions* thus requires the termination of the current action plan whilst rapidly selecting a viable alternative (Mars and others 2009; Neubert and others 2010; Neubert and others 2011). One can easily see how this requires several control processes, that likely overlap in time (Fig. 6). First, the currently prepared action needs to be prevented from release. Second, the inhibitory influence on action alternatives needs to be halted, or possibly reversed. Third, the new action needs to be prepared.

Neubert and others (2011), for example, could show a sustained intracortical inhibition for both selected and non-selected action representations during simple preparation

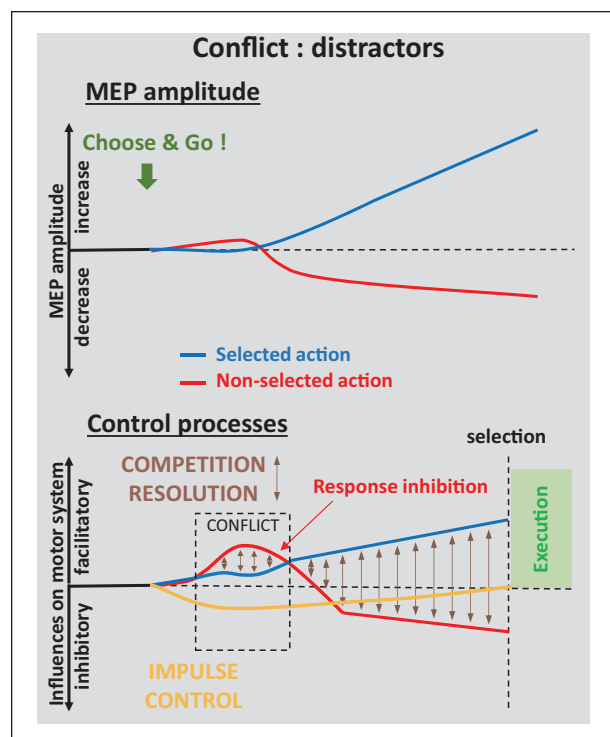


Figure 5. Hypothetical motor-evoked potential (MEP) changes and control processes during sensory conflict. In the presence of conflicting sensory information, MEPs are initially facilitated for the nonselected action. This MEP facilitation then decreases such that nonselected MEPs are suppressed when measured later on in the trial, closer to movement. The occurrence of sensory conflict is thought to trigger an initial and automatic activation of the invalid action representation. Conflict resolution then relies on the inhibition of this erroneous activation, leading to suppression of the nonselected action representation, as indeed seen in MEPs. Note that the initial conflict-related facilitation of nonselected MEPs suggests that irrelevant representations are less influenced by impulse control. This contrasts with the common observation made for the representation of relevant actions that are ultimately selected in no-conflict trials (see Fig. 3). Importantly, the studies that looked at MEPs in conflict trials do not show the (impulse control) inhibition of the selected action representation, although recent data suggest that this process may be boosted when a conflict is expected compared to when it is unexpected (Klein and others 2014). The timeline is for illustration purposes only and does not reflect the true timecourse of process deployment.

trials. However, on trials requiring reprogramming of a prepared action, a steep decrease in this inhibitory influence (in form of a release from intracortical inhibition) was observed. This suggests that the regulation of intracortical inhibition, possibly specific for the hand required for the new response, plays a key role in action reprogramming, with recent evidence suggesting that some form of inhibitory control may even be deployed when merely observing visual information that triggers a change in an observed movement (Janssen and others 2015).

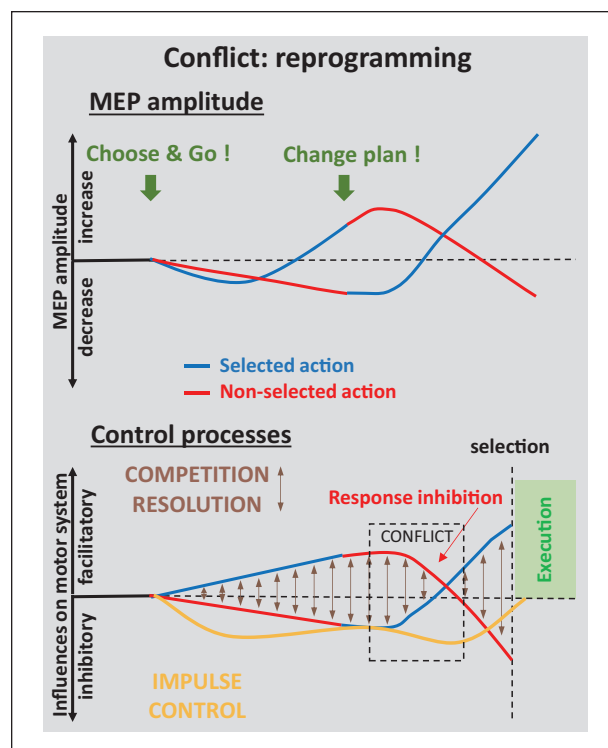


Figure 6. Hypothetical motor-evoked potential (MEP) changes and control processes during reprogramming. When additional sensory information requires a sudden change in action (“Change plan!”), the initially selected action representation needs to be suppressed, while quickly ensuring that the activation of the alternative, and initially suppressed, action representation is boosted. Presumably, impulse control needs to be redeployed following the change in action plan, but note that currently no evidence is available on the time course of impulse control nor its effect on MEPs in this context. Previous work suggests that the newly required action is selected through a release from inhibition (Neubert and others 2010). However, the precise time course of MEP amplitude following a “change plan” instruction remains undetermined. Comparing MEPs for selected and nonselected actions halfway through reprogramming, for example, may look as if no differences between the two representations exists. As in previous examples, we point out again that divorcing inhibitory control related to action reprogramming from impulse control and competition resolution, for example, can be accomplished by probing intracortical and transcortical circuits directly using paired-pulse and double-coil transcranial magnetic stimulation (TMS) protocols (Neubert and others 2010). The timeline is for illustration purposes only and does not reflect the true time course of process deployment.

The control of these changes likely originates from several regions generally linked to conflict control. Each of these regions can have specific, and even opposite influences on MEPs during action reprogramming. For example, facilitatory influences on MEP amplitude have been shown to arise from the pre-supplementary motor area (Buch and others 2010), while the right inferior frontal gyrus seems to

exert an inhibitory influence on MEPs, albeit at a later time point than the pre-supplementary motor area (Buch and others 2010; Neubert and others 2010).

Conflict Arising from New Sensory Information that Requires Stopping

Many situations require us to abort an action plan or halt an ongoing movement altogether. For example, a motor-bike approaching unexpectedly when crossing a busy street requires to quickly abort ones stride to avoid a collision.

Experimentally, the psychological processes and neural mechanisms for aborting a prepared action have often been studied with the stop signal task, in which an explicit stop-signal occurs at some point during the task (reviewed in (Boucher and others 2007; Verbruggen and Logan 2008). TMS-induced MEPs decrease following the presentation of a stop-signal (Greenhouse and others 2012; van den Wildenberg and others 2010), thus providing a physiological marker for the deployment of an inhibitory process (Majid and others 2012). Moreover, paired-pulse TMS protocols show that TMS-derived assays of intracortical inhibition are increased on stop-trials, relative to go-trials, just prior to movement onset (Coxon and others 2006).

In the standard stop signal task, the effect of aborting a selected response appears to have a global suppressive effect on the motor system. That is, successful stopping not only reduces MEPs in the task-relevant agonist muscle but also reduces MEPs in task-irrelevant muscles (Fig. 7). For example, when the task requires stopping an index finger response, MEP suppression is observed in other muscles of the upper (Coxon and others 2006; van den Wildenberg and others 2010) and lower extremities (Badry and others 2009; Greenhouse and others 2012; Majid and others 2012).

The idea that a stop signal triggers a global stop command is consistent with the observation that people show difficulty in variants of the stop signal task requiring to only abort one component of a multiresponse action. For example, a stop signal may require aborting only one hand response in a bimanual task; the other hand has to respond even if a stop signal appears. In such selective-stop tasks, reaction times for the nonstopped hand are slower on stop trials compared to go trials (Aron and Verbruggen 2008; Coxon and others 2007). This deficit in stopping can be overcome with advance information regarding the action that might be aborted (Aron and Verbruggen 2008). Under such conditions, no selective stop costs occur for the nonstopped hand. Moreover, TMS here indicates more focal suppression of the stopped effector representation in M1 (Majid and others 2012). One proposal recently brought forward is that distinct neural pathways govern global or selective

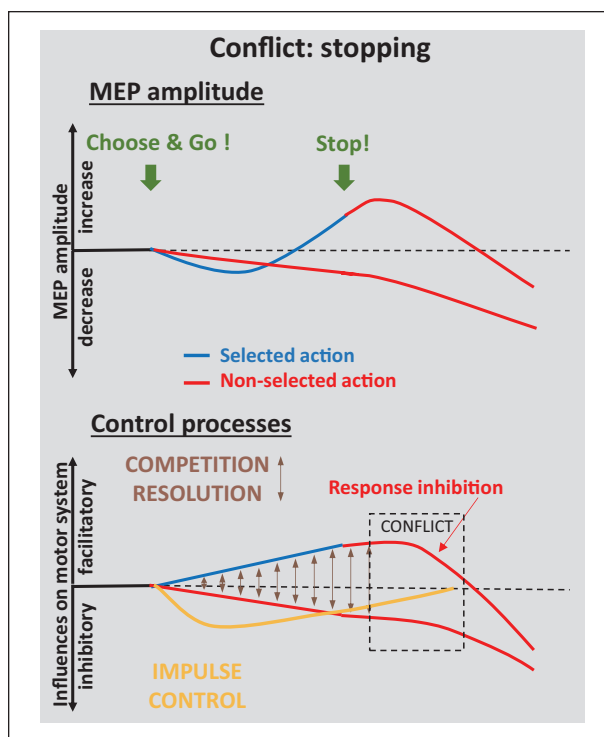


Figure 7. Hypothetical motor-evoked potential (MEP) changes and cognitive control processes during stopping. When additional sensory information requires to suddenly stop an action ("Stop!"), the initially selected action representation needs to be suppressed, as seen in MEPs. In most situations, this response inhibition seems to work in a nonspecific way, suppressing globally the motor cortex, irrespective of the effector involved in the task. That is, the MEP suppression concerns both the selected and nonselected actions, and even irrelevant action representations, consistent with the operation of a global inhibition process to allow a fast interruption of the initially programmed action. Presumably, impulse control is released after the stop signal as the activation of the selected action representation becomes suppressed by the response inhibition process, reducing thus the need for a safeguard against premature responding. Yet note that currently no evidence is available on the time course of impulse control in this context. The timeline is for illustration purposes only and does not reflect the true time course of process deployment.

reactive stopping (Aron 2011). This also illustrates how stopping can be further decomposed into distinct subprocesses, with distinct physiological influences on the human motor system.

To summarize, MEPs have been used to assay how various forms of response conflict influence action representations prior to movement. While some of the specific interactions between processes involved in conflict and MEPs remain undetermined (Figs. 5-7), these studies have demonstrated some of the distinct influences exerted on action representations during different types of conflict.

Decision Making and Motor-Evoked Potentials

As recently argued (Bestmann and Krakauer 2015), MEPs elicited by stimulation over M1 can contain contributions from transcortical signals. In this section, we ask how MEPs can be used to assay the contribution that transcortical pathways exert on the motor system during decision making.

Transcortical influences on MEPs may arise from the direct stimulation of neurons in a nearby area (e.g., PMd), or to the stimulation of axons projecting from frontal, parietal, and subcortical regions to (pre)motor cortex (Fig. 2, Box 1). This predicts that MEPs are amenable to influences from decision-related variables such as prior probabilities, subjective expected values or simply sensory evidence, which are computed elsewhere but influence action representations. Recent proposals argue that this allows motor regions to answer to the question “If I would have to move now, what choice of action should I make” (Cisek and Pastor-Bernier 2014; Hanks and others 2015). One appealing feature of MEPs in humans is that they allow us to “listen” to how motor regions would answer this question, by quantifying their state in an effector- and muscle-specific way, and potentially with physiological read-outs that are underpinned by distinct inhibitory and excitatory circuits (see Box 1 for discussion).

Several recent studies exemplify this idea, and we here briefly discuss examples for decision-related variables including value, biomechanical cost and motivation (Chiu and others 2014; Cos and others 2014; Freeman and others 2014; Klein-Flügge and Bestmann 2012; Klein-Flügge and others, 2013; Klein and others 2012).

When preparing actions based on the subjective value associated with different alternatives, variations in MEP amplitudes distinguish between selected versus nonselected actions in that MEPs increase for the selected and decrease for the nonselected action (see Fig. 3b in Klein-Flügge and Bestmann 2012). As mentioned above, this provides evidence for competition resolution, but on its own would not allow for isolating the influence of the value decision process. To achieve this, the authors estimated the subjective expected value of choice options using a computational model, cumulative prospect theory. This allowed for inferring how much more worth one option was to participants over the alternative. Using these estimates, the authors showed that MEPs and reaction times varied as a function of the difference in subjective value that participants assigned to the selected and nonselected options. Importantly, the separation between selected and nonselected actions emerged even before the actual decision process was complete (see Fig. 4 in Klein-Flügge and Bestmann 2012). This finding is in support of the view that the continuous shaping of action representations already during

the decision period may reflect an answer to the question “if I had to move now, what would I do” (Hanks and others 2015). MEPs then can provide a readout of how internal decision processes contribute to resolving which course of action to take.

Similarly, Klein and others (2012) measured MEPs while participants performed a task that required them to choose between two finger responses according to the color of an imperative signal; importantly, the muscle from which MEPs were recorded was either associated with a favorable or a neutral monetary reward. The authors found a global MEP up-regulation in the biased compared to the neutral condition. This effect was already evident at the onset of the imperative signal and further strengthened during the course of action preparation (see Fig. 6ab in Klein and others 2012). The reward effect on MEPs correlated with the subjects’ behavior, suggesting a relationship between this reward effect on motor activity and the preferences subjects displayed when making their choices (see Fig. 6c in Klein and others 2012).

Another relevant factor that determines the overall value of an action is the cost associated with its execution. When humans make free choices between reaching actions, they tend to choose the one that is biomechanically easiest (Cos and others 2014). This suggests that we are able to predict, prior to movement initiation, the biomechanical properties of different movement alternatives and choose the one associated with the lowest total energetic cost. Consistently, the amplitude of MEPs is initially inversely proportional to the biomechanical cost of the action, that is, larger for the less effortful action (see Fig. 4a in Cos and others 2014). Subsequently, once the decision is made, MEPs begin to reflect the biomechanical requirements of the action (larger for biomechanically more demanding actions). This suggests that MEP changes initially track the competition between different candidate actions, but then reflect the processes of preparing the chosen action.

Stimuli that reliably predict rewards may also trigger action tendencies, whereas aversive stimuli may trigger automatic tendencies to withhold movements. One possibility is that such influences are expressed at the level of the motor system and directly influence action representations there. Indeed, Chiu and others (2014) recently confirmed this idea, by showing that appetitive cues bias our tendencies to act, and that this is paralleled by increases in MEP amplitudes. By contrast, aversive cues decrease one’s propensity to act, and this in turn is mirrored in relative MEP decreases. This again demonstrates that motivational information can influence action representations in specific ways, prior to the actual execution of that action.

Interestingly, Freeman and others (2014) recently demonstrated that motivational stimuli can increase MEP

amplitudes across several muscles, even in task-irrelevant ones. On the other hand, stimuli that predict an absence of reward, and presumably do not trigger motivational action tendencies, do not reveal this effect. By contrast, when participants are explicitly instructed not to move (no-go trials), regardless of the stimuli presented, a relative MEP suppression occurs for rewarding but not unrewarding stimuli. This effect may help to mitigate the action tendency elicited by reliably rewarding stimuli. Interestingly, while there is an overall increase in MEP amplitude on go trials, the relative suppression observed for no-go trials is restricted to the effector that can obtain the reward. Some form of impulse control may thus prevent responses on no-go trials, but specifically so in effectors for which rewarding stimuli are likely to trigger an automatic action tendency.

Collectively, these results serve to illustrate that influences on action representations are not just stimulus driven, but that dynamic adjustments of motor representations also occur during internal decision processes. MEPs do not provide insight into the anatomical routes mediating these influences. It is likely though that in different contexts, distinct anatomical pathways mediate influences on MEPs. This would provide a flexible mechanism for continuous updating of action representations, based on the requirements of the current situation, which can potentially be assessed and quantified with MEP recordings in human participants.

Conclusions

Motor-evoked potentials elicited with TMS over human M1 provide unique physiological read-outs of the dynamic changes in action representations during behavior. An emerging picture is that MEPs are sensitive to influences from different control mechanisms, including high-level cognition and decision making, which jointly shape the activity of the motor output system during action preparation. Increasingly, human TMS studies identify the temporal specificity of these influences as well as the routes they take with regards to intracortical inhibitory and excitatory circuits, and even the specific transcortical pathways through which they exert their control.

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References

- Aron AR. 2011. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biol Psychiatry* 69(12):e55–68.
- Aron AR, Verbruggen F. 2008. Stop the presses: dissociating a selective from a global mechanism for stopping. *Psychol Sci* 19(11):1146–53.
- Badry R, Mima T, Aso T, Nakatsuka M, Abe M, Fathi D, and others. 2009. Suppression of human cortico-motoneuronal excitability during the Stop-signal task. *Clin Neurophysiol* 120(9):1717–23.
- Bestmann S, Harrison LM, Blankenburg F, Mars RB, Haggard P, Friston KJ, and others. 2008. Influence of uncertainty and surprise on human corticospinal excitability during preparation for action. *Curr Biol* 18(10):775–80.
- Bestmann S, Krakauer JW. 2015. The uses and interpretations of the motor-evoked potential for understanding behaviour. *Exp Brain Res* 233(3):679–89.
- Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402(6758):179–81.
- Boucher L, Palmeri TJ, Logan GD, Schall JD. 2007. Inhibitory control in mind and brain: an interactive race model of countermanding saccades. *Psychol Rev* 114(2):376–97.
- Buch ER, Mars RB, Boorman ED, Rushworth MF. 2010. A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. *J Neurosci* 30(4):1395–401.
- Burle B, Vidal F, Tandonnet C, Hasbroucq T. 2004. Physiological evidence for response inhibition in choice reaction time tasks. *Brain Cogn* 56(2):153–64.
- Chen R, Hallett M. 1999. The time course of changes in motor cortex excitability associated with voluntary movement. *Can J Neurol Sci* 26(3):163–9.
- Chen R, Yaseen Z, Cohen LG, Hallett M. 1998. Time course of corticospinal excitability in reaction time and self-paced movements. *Ann Neurol* 44(3):317–25.
- Chiu YC, Cools R, Aron AR. 2014. Opposing effects of appetitive and aversive cues on go/no-go behavior and motor excitability. *J Cogn Neurosci* 26(8):1851–60.
- Cisek P. 2007. Cortical mechanisms of action selection: the affordance competition hypothesis. *Philos Trans R Soc Lond B Biol Sci* 362(1485):1585–99.
- Cisek P. 2012. Making decisions through a distributed consensus. *Curr Opin Neurobiol* 22(6):927–36.
- Cisek P, Kalaska JF. 2005. Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. *Neuron* 45(5):801–14.
- Cisek P, Pastor-Bernier A. 2014. On the challenges and mechanisms of embodied decisions. *Philos Trans R Soc Lond B Biol Sci* 369(1655):20130479.
- Cohen JD, Dunbar K, McClelland JL. 1990. On the control of automatic processes: a parallel distributed processing account of the Stroop effect. *Psychol Rev* 97(3):332–61.

- Cos I, Duque J, Cisek P. 2014. Rapid prediction of biomechanical costs during action decisions. *J Neurophysiol* 112(6):1256–66.
- Coxon JP, Stinear CM, Byblow WD. 2006. Intracortical inhibition during volitional inhibition of prepared action. *J Neurophysiol* 95(6):3371–83.
- Coxon JP, Stinear CM, Byblow WD. 2007. Selective inhibition of movement. *J Neurophysiol* 97(3):2480–9.
- Davey NJ, Rawlinson SR, Maskill DW, Ellaway PH. 1998. Facilitation of a hand muscle response to stimulation of the motor cortex preceding a simple reaction task. *Motor Control* 2(3):241–50.
- Davranche K, Tandonnet C, Burle B, Meynier C, Vidal F, Hasbroucq T. 2007. The dual nature of time preparation: neural activation and suppression revealed by transcranial magnetic stimulation of the motor cortex. *Eur J Neurosci* 25(12):3766–74.
- Di Lazzaro V, Rothwell JC. 2014. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. *J Physiol* 592(Pt 19):4115–28.
- Di Lazzaro V, Ziemann U. 2013. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. *Front Neural Circuits* 7:18.
- Duclos Y, Schmied A, Burle B, Burnet H, Rossi-Durand C. 2008. Anticipatory changes in human motoneuron discharge patterns during motor preparation. *J Physiol* 586(4):1017–28.
- Duque J, Ivry RB. 2009. Role of corticospinal suppression during motor preparation. *Cereb Cortex* 19(9):2013–24.
- Duque J, Labruna L, Cazaes C, Ivry RB. 2014. Dissociating the influence of response selection and task anticipation on corticospinal suppression during response preparation. *Neuropsychologia* 65:287–96.
- Duque J, Labruna L, Verset S, Olivier E, Ivry RB. 2012. Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. *J Neurosci* 32(3):806–816.
- Duque J, Lew D, Mazzocchio R, Olivier E, Ivry RB. 2010. Evidence for two concurrent inhibitory mechanisms during response preparation. *J Neurosci* 30(10):3793–802.
- Duque J, Mazzocchio R, Dambrosia J, Murase N, Olivier E, Cohen LG. 2005. Kinematically specific interhemispheric inhibition operating in the process of generation of a voluntary movement. *Cereb Cortex* 15(5):588–93.
- Duque J, Olivier E, Rushworth M. 2013. Top-down inhibitory control exerted by the medial frontal cortex during action selection under conflict. *J Cogn Neurosci* 25(10):1634–48.
- Freeman SM, Razhas I, Aron AR. 2014. Top-down response suppression mitigates action tendencies triggered by a motivating stimulus. *Curr Biol* 24(2):212–6.
- Greenhouse I, Oldenkamp CL, Aron AR. 2012. Stopping a response has global or nonglobal effects on the motor system depending on preparation. *J Neurophysiol* 107(1):384–92.
- Greenhouse I, Saks D, Hoang T, Ivry RB. 2015. Inhibition during response preparation is sensitive to response complexity. *J Neurophysiol* 113(7):2792–800.
- Hamada M, Galea JM, Di Lazzaro V, Mazzone P, Ziemann U, Rothwell JC. 2014. Two distinct interneuron circuits in human motor cortex are linked to different subsets of physiological and behavioral plasticity. *J Neurosci* 34(38):12837–49.
- Hanks TD, Kopec CD, Brunton BW, Duan CA, Erlich JC, Brody CD. 2015. Distinct relationships of parietal and prefrontal cortices to evidence accumulation. *Nature* 520(7546):220–3.
- Hasan A, Galea JM, Casula EP, Falkai P, Bestmann S, Rothwell JC. 2013. Muscle and timing-specific functional connectivity between the dorsolateral prefrontal cortex and the primary motor cortex. *J Cogn Neurosci* 25:558–70.
- Hasbroucq T, Kaneko H, Akamatsu M, Possamai CA. 1997. Preparatory inhibition of cortico-spinal excitability: a transcranial magnetic stimulation study in man. *Brain Res Cogn Brain Res* 5(3):185–92.
- Hasbroucq T, Kaneko H, Akamatsu M, Possamai CA. 1999. The time-course of preparatory spinal and cortico-spinal inhibition: an H-reflex and transcranial magnetic stimulation study in man. *Exp Brain Res* 124(1):33–41.
- Hasbroucq T, Osman A, Possamai CA, Burle B, Carron S, Dépy D, and others. 1999. Cortico-spinal inhibition reflects time but not event preparation: neural mechanisms of preparation dissociated by transcranial magnetic stimulation. *Acta Psychol (Amst)* 101(2-3):243–66.
- Janssen L, Steenbergen B, Carson RG. 2015. Anticipatory planning reveals segmentation of cortical motor output during action observation. *Cereb Cortex* 25(1):192–201.
- Klein-Flügge MC, Bestmann S. 2012. Time-dependent changes in human corticospinal excitability reveal value-based competition for action during decision processing. *J Neurosci* 32(24):8373–82.
- Klein-Flügge MC, Nobbs D, Pitcher JB, Bestmann S. 2013. Variability of human cortico-spinal excitability tracks the state of action preparation. *J Neurosci* 33(13):5564–5572.
- Klein PA, Olivier E, Duque J. 2012. Influence of reward on corticospinal excitability during movement preparation. *J Neurosci* 32(50):18124–36.
- Klein PA, Petitjean C, Olivier E, Duque J. 2014. Top-down suppression of incompatible motor activations during response selection under conflict. *Neuroimage* 86:138–49.
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, and others. 1993. Corticocortical inhibition in human motor cortex. *J Physiol* 471:501–19.
- Labruna L, Lebon F, Duque J, Klein PA, Cazaes C, Ivry RB. 2014. Generic inhibition of the selected movement and constrained inhibition of nonselected movements during response preparation. *J Cogn Neurosci* 26(2):269–78.
- Lebon F, Greenhouse I, Labruna L, Vanderschelden B, Papaxanthi C, Ivry RB. 2015. Influence of delay period duration on inhibitory processes for response preparation. *Cereb Cortex*. Epub ahead of print. April 16. doi:10.1093/cercor/bhv069.
- Leocani L, Cohen LG, Wassermann EM, Ikoma K, Hallett M. 2000. Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. *Brain* 123 (Pt 6):1161–73.
- Majid DS, Cai W, George JS, Verbruggen F, Aron AR. 2012. Transcranial magnetic stimulation reveals dissociable mechanisms for global versus selective corticomotor suppression

- underlying the stopping of action. *Cereb Cortex* 22(2): 363–71.
- Mars RB, Bestmann S, Rothwell JC, Haggard P. 2007. Effects of motor preparation and spatial attention on corticospinal excitability in a delayed-response paradigm. *Exp Brain Res* 182(1):125–9.
- Mars RB, Klein MC, Neubert FX, Olivier E, Buch ER, Boorman ED and others. 2009. Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. *J Neurosci* 29(21):6926–31.
- Michelet T, Duncan GH, Cisek P. 2010. Response competition in the primary motor cortex: corticospinal excitability reflects response replacement during simple decisions. *J Neurophysiol* 104(1):119–27.
- Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF. 2010. Cortical and subcortical interactions during action reprogramming and their related white matter pathways. *Proc Natl Acad Sci U S A* 107(30):13240–5.
- Neubert FX, Mars RB, Olivier E, Rushworth MF. 2011. Modulation of short intra-cortical inhibition during action reprogramming. *Exp Brain Res* 211(2):265–76.
- Opie GM, Ridding MC, Semmler JG. 2014. Task-related changes in intracortical inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation. *J Neurophysiol* 113(5):1470–9.
- Prut Y, Fetz EE. 1999. Primate spinal interneurons show pre-movement instructed delay activity. *Nature* 401(6753): 590–4.
- Reynolds C, Ashby P. 1999. Inhibition in the human motor cortex is reduced just before a voluntary contraction. *Neurology* 53(4):730–5.
- Ridderinkhof KR. 2002. Micro- and macro-adjustments of task set: activation and suppression in conflict tasks. *Psychol Res* 66(4):312–23.
- Rushworth MF, Mars RB, Summerfield C. 2009. General mechanisms for making decisions? *Curr Opin Neurobiol* 19(1):75–83.
- Selen LP, Shadlen MN, Wolpert DM. 2012. Deliberation in the motor system: reflex gains track evolving evidence leading to a decision. *J Neurosci* 32(7):2276–86.
- Sinclair C, Hammond GR. 2008. Reduced intracortical inhibition during the foreperiod of a warned reaction time task. *Exp Brain Res* 186(3):385–92.
- Sinclair C, Hammond GR. 2009. Excitatory and inhibitory processes in primary motor cortex during the foreperiod of a warned reaction time task are unrelated to response expectancy. *Exp Brain Res* 194(1):103–13.
- Starr A, Caramia M, Zarola F, Rossini PM. 1988. Enhancement of motor cortical excitability in humans by non-invasive electrical stimulation appears prior to voluntary movement. *Electroencephalogr Clin Neurophysiol* 70(1):26–32.
- Tandonnet C, Garry MI, Summers JJ. 2011. Selective suppression of the incorrect response implementation in choice behavior assessed by transcranial magnetic stimulation. *Psychophysiology* 48(4):462–9.
- Taylor PC, Nobre AC, Rushworth MF. 2007. Subsecond changes in top down control exerted by human medial frontal cortex during conflict and action selection: a combined transcranial magnetic stimulation electroencephalography study. *J Neurosci* 27(42):11343–53.
- Thura D, Cisek P. 2014. Deliberation and commitment in the premotor and primary motor cortex during dynamic decision making. *Neuron* 81(6):1401–16.
- Touge T, Taylor JL, Rothwell JC. 1998. Reduced excitability of the cortico-spinal system during the warning period of a reaction time task. *Electroencephalogr Clin Neurophysiol* 109(6):489–95.
- van Campen AD, Keuken MC, van den Wildenberg WP, Ridderinkhof KR. 2014. TMS over M1 reveals expression and selective suppression of conflicting action impulses. *J Cogn Neurosci* 26(1):1–15.
- van den Hurk P, Mars RB, van Elswijk G, Hegeman J, Pasman JW, Bloem BR and others. 2007. Online maintenance of sensory and motor representations: effects on corticospinal excitability. *J Neurophysiol* 97(2):1642–8.
- van den Wildenberg WP, Burle B, Vidal F, van der Molen MW, Ridderinkhof KR, Hasbroucq T. 2010. Mechanisms and dynamics of cortical motor inhibition in the stop-signal paradigm: a TMS study. *J Cogn Neurosci* 22(2): 225–39.
- Verbruggen F, Logan GD. 2008. Response inhibition in the stop-signal paradigm. *Trends Cogn Sci* 12(11):418–24.
- Verleger R, Kuniecki M, Moller F, Fritzmanna M, Siebner HR. 2009. On how the motor cortices resolve an inter-hemispheric response conflict: an event-related EEG potential-guided TMS study of the flankers task. *Eur J Neurosci* 30(2):318–26.
- Wong AL, Haith AM, Krakauer JW. 2014. Motor planning. *Neuroscientist*. Epub ahead of print. June 30, 2014. doi:10.1177/1073858414541484.